

The University of Chicago

I. THE ADDITION OF HYDROGEN BROMIDE TO
BUTENE-1, ISOBUTYLENE AND PENTENE-1

II. THE PREPARATION OF SEVERAL INTERMEDI-
ATES IN THE SYNTHESIS OF 1-(3, 4-DIHYDROXY-
PHENYL)-1-HYDROXY-2-AMINOPROPANE

A DISSERTATION SUBMITTED TO THE FACULTY OF THE
DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1941

By

JOHN A. HINCKLEY, JR.

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THE ADDITION OF HYDROGEN BROMIDE TO
BUTENE-1, ISOBUTYLENE AND PENTENE-1

INTRODUCTION

Markovnikov¹ in 1870 published the generalization that in the addition of halogen acids to olefins the halogen atom becomes attached (a) to the carbon atom carrying the lesser number of hydrogen atoms, or (b) in the case of unsaturated halides, to the carbon atom already carrying the halogen. This rule was useful in predicting the direction of addition of hydrogen chloride, hydrogen iodide, and in some cases, of hydrogen bromide to unsaturated compounds.

In the literature dealing with the addition of hydrogen bromide to unsaturated compounds a great many discrepancies existed. Previous to 1933, observations of the direction of addition of hydrogen bromide to allyl bromide were particularly confusing because of their lack of agreement. Clark and Gray,² for instance, describe the effect of a magnetic field in increasing the yield of 1,2 dibromopropane, and Wibaut³ found that solvent, heat, and light were the important factors in determining the direction of addition.

In 1933 the study of the factors affecting the addition of

¹Markovnikov, Ann, 153, 256 (1870).

²Clark and Gray, Trans. Roy. Soc. Can., 37, 24, sec. 3, 111 (1930).

³Wibaut, Rec. Trav. Chim., 50, 313 (1931).

hydrogen bromide to allyl bromide, of Kharasch and Mayo¹ was published. It was shown conclusively that 1,2-dibromopropane was the normal reaction product, but that under the influence of oxygen or peroxides, 1,3-dibromopropane was formed. The normal reaction was very slow and the peroxide catalyzed reaction rapid. This discovery served to clarify the previous confusion, and indicated that varying quantities of peroxides contained in the allyl bromide had been responsible for the varying results obtained by other authors.

In the same year the results of a study² of the addition of hydrogen bromide to vinyl bromide was published. It was shown that 1,1-dibromoethane was the normal product of the reaction, and was obtained in 100 per cent yields by carefully excluding air and peroxide from the reaction mixture. 1,2-dibromoethane was formed in 100 per cent yields when the reaction took place under the influence of peroxides.

In contrast to the lack of agreement in the literature dealing with the reactions of hydrogen bromide with allyl bromide and vinyl bromide, observations on the reaction of propylene with hydrogen bromide were uniform in that n-propyl bromide had never been found in the reaction products. Isopropyl bromide was the only reaction product reported.

Kharasch, McNab, and Mayo³ in 1933, showed that in the presence of added peroxides, for example, ascaridol, practically

¹Kharasch and Mayo, J. Am. Chem. Soc., **55**, 2468 (1933).

²Kharasch, McNab, and Mayo, ibid., p. 2521.

³Ibid., p. 2531.

quantitative yields of n-propyl bromide are obtained from propylene and hydrogen bromides. It was observed that this reaction, compared to those of allyl bromide and vinyl bromide, was relatively insensitive to the peroxide effect. The presence of air or oxygen did not give high yields of the abnormal compound, as was observed with the peroxide sensitive allyl bromide and vinyl bromide reactions.

Vinyl chloride was found to behave similarly to the vinyl bromide in that high yields of the 1-bromo, 1-chloroethane were obtained under peroxide-free conditions, and high yields of 1-bromo 2-chloroethane were obtained under the influence of air or added peroxides.¹

PREVIOUS WORK

Very few references to the reactions of halogen acids with butene-1 occur in the literature. Lieben and Rossi² and Saytzeff³ in 1871 recorded the observation that butene-1 and hydrogen iodide react to form 2-iodobutane. In 1930 Lucas and co-workers⁴ found 2-bromobutane to be the only product of the reaction of hydrogen bromide with butene-1 in glacial acetic acid. Coffin, Sutherland, and Maass⁵ found that hydrogen chloride and butene-1 gave only 2-chlorobutane. Shane⁶ obtained only 2-bromo-

¹Kharasch and Hannum, ibid., 56, 712 (1934).

²Lieben and Rossi, Ann., 158, 164 (1871).

³Saytzeff, J. Prakt. Chem., 111, 88 (1871).

⁴Lucas, Dillon, and Young, J. Am. Chem. Soc., 52, 1949 (1930).

⁵Coffin, Sutherland, and Maass, Can. J. Res., 2, 267 (1930).

⁶Shane, Ph.D. Dissertation, University of Chicago (1933).

butane from the reaction of hydrogen bromide with butene-1.

The agreement in the literature concerning the direction of addition of the hydrogen bromide to isobutylene, is practically complete. Tert-butyl bromide has been found exclusively by Brunel,¹ Michael and Zeidler,² and Roozebroom.³ Ipatieff and Ogonowsky⁴ state that by working in acetic acid solution small amounts, namely 5 and 16 per cent, in two experiments, of isobutyl bromide were obtained. As will be seen later, this unusual result was probably due to errors in the method of analysis or impurities in the starting materials or both. R. S. Shane⁵ in this laboratory found that tert-butyl bromide was formed exclusively under a variety of conditions.

Ingold and Ramsden⁶ in studying the addition of hydrogen bromide to pentene-1 found only 2-bromopentane as the product, when the reaction was carried out under a variety of conditions. Sherrill, Mayer, and Walter⁷ in a paper published in 1934, after the first papers by Kharasch and co-workers had been published, stated their belief that the peroxide effect was largely overrated in importance as a factor influencing the addition of hydrogen bromide to olefins, and gave various arguments, cited some data,

¹Brunel, J. Am. Chem. Soc., 39, 1990 (1917).

²Michael and Zeidler, Ann., 393, 109 (1912).

³Roozebroom, Ber., 14, 2396 (1881).

⁴Ipatieff and Ogonowsky, Ber., 36, 1988 (1903).

⁵Shane, op. cit.

⁶Ingold and Ramsden, J. Chem. Soc., 2752 (1931).

⁷Sherrill, Mayer, and Walter, J. Am. Chem. Soc., 56, 926 (1934).

and reported a few experiments to substantiate this position. Specifically, they claimed to have shown that (a) 1-bromopentane was formed from pentene-1 when the reaction was carried out in organic solvents and (b) that 2-bromopentane was formed when the hydrogen bromide was contained in water solution.

T. M. Beck¹ found only 2-bromopentane as the product of the reaction under a variety of conditions.

PRESENT STUDY

The results of a number of experiments with hydrogen bromide and butene-1 are given in Table 1. These experiments lead to the conclusion that unless a peroxide such as ascaridole or benzoyl peroxide is present during the reaction, 2-bromobutane is formed practically quantitatively. Neither air nor ozone has an appreciable effect on the normal reaction. Both the normal and the peroxide catalyzed reactions take place very rapidly, and it is reasonable to expect that, unless substantial amounts of peroxides are present in the reaction mixture during the time that the hydrogen bromide is added to the butene-1, the normal reaction will take place to the greater extent. The lack of effectiveness of peroxide, present in the reaction tube but not in solution, in the butene-1, is demonstrated by run number 6 in Table 1. The normal product was obtained. The butene-1 was condensed in the reaction tube, the ascaridol added, with no particular effort made to dissolve the ascaridol in the butene-1, and the hydrogen bromide was rapidly added. A lack of homogeneity was noted during the time that the hydrogen bromide was added. Apparently

¹T. M. Beck, Ph.D. Dissertation, University of Chicago (1933).

TABLE 1
ADDITION OF HYDROGEN BROMIDE TO BUTENE-1

Run Number	Grams Butene-1	Grams HBr	Grams Catalyst	Grams Solvent	Hours Reaction Time	Product Yield Percentage	Refractive Index Product	Boiling Point of Product versus Percentage Distilled				Percentage 1-Bromobutane in Product	
								10%	30%	70%	90%	n_D^{20}	b.p.
1	4.0	10.0	1/2 Thiocresol .01 $MnCl_2$	13.6 Pentane	90	69	1.4361	87.7	89.2	89.9	90.5	0	5
2	18.4	40	1.5 Diphenyl Amine ^a		5.5	64	1.4369	90.5	90.6	90.6	90.6	0	0
3	9.8	25.9	1.3 Dicyclo hexylamine oxide		4.5	51	1.4368	90.6	90.7	90.8	90.8	0	0
4	9.3	24.1	Saturated with O_2		4	37	1.4369	90.4	90.4	90.4	...b	0	0
5	5.6	9.1	Small Amount Ozone ^c		3	42	1.4366	90.6	91.2	91.7	95.0	0	5
6	9.2	19.5	1.5 Ascaridole		3	54	1.4369	90.0	90.0	90.4	93.8	0	5
7	9.0	22.6	1.6 Ascaridole	8.1 Pentane	3.5	76	1.4396	101.1	101.2	101.2	101.5	100	100
8	5.7	13.8	1.7 Ascaridole		3.5	95	1.4395	99.0	99.9	101.5	102.2	100	95
9	3.4	8.1	1.5 Ascaridole		17	89	1.4391	97.9	98.9	101.5	102.8	85	95
10	12.1	31.3	2.0 Ascaridole		4	80	1.4390	97.2	99.1	100.5	101.1	80	90
11	10.3	23.0	1.4 Benzoyl Peroxide		4	80	1.4390	93.3	97.5	100.4	100.7	80	80

^aIn vacuo.

^bHoldup of column too great to determine 90 per cent temperature.

^cAir which had been treated in ozonizer passed through contents of tube for 1/2 hour at -80°C.

the reaction took place almost as fast as the hydrogen bromide was introduced into the tube, with the ascaridol not in solution and therefore ineffective.

This explanation of the unexpected result of this experiment is borne out by the results of the balance of the peroxide runs in which solution of the peroxide in the butene-1 was attained by thorough mixing, before the addition of the hydrogen bromide. The hydrogen bromide was added slowly and the reaction mixture frequently examined to see that homogeneity was maintained.

It is probable that the failure of Shane¹ to obtain 1-bromobutane was due to the absence of peroxides in the butene-1 during the addition of hydrogen bromide, inasmuch as the relatively insoluble benzoyl peroxide was used exclusively. However, the effectiveness of this peroxide, if particular care is taken to dissolve it, at least partially, in the butene-1, is shown by run number 11 in Table 1.

In Table 1 the total yield of butyl bromides is given under the heading "Product Yield." This is based on the butene-1 used. In the column headed "Boiling Point of Product versus Percentage Distilled," are given the vapor temperatures observed during the fractional distillation of the butyl bromides at the points at which 10, 30, 70, and 90 volume percentages, respectively, had been distilled off. Under the "Percentage 1-Bromobutane in Product" column are given the results of the analyses of the butyl bromides. The differences between the figures given for 1-bromobutane percentage and 100 per cent are the percentages of 2-bromobutane. The 1-bromobutane percentage is calculated in two ways,

¹Shane, op. cit.

the first, given under subheading " n_D^{20} ", from the refractive index of the butyl bromide product, assuming that the refractive index of a mixture of 1 and 2-bromobutanes is a first-degree function of the refractive indices of the pure components, as given later under "Experimental Part." The second column of figures under "Percentage 1-Bromobutane" and under subheading "b.P." is obtained from a consideration of the vapor temperatures observed during the fractional distillation of the product. By plotting the vapor temperatures against the percentage distilled over, the point at which the lower boiling 2-bromobutane has practically all distilled over and the 1-bromobutane has started to distill over is made obvious by the rather sharp rise in temperature. The volume of bromobutane that has come over up to the point at which the vapor temperature is the average of the boiling points of the two pure components is considered, as is the usual practice in this respect, to be the volume of the lower boiling component, 2-bromobutane, and the remaining volume to be that of the 1-bromobutane occurring in the original mixture. This method of analysis does not depend upon the assumption that a binary mixture is dealt with. The selection of the average temperature as the point of division is somewhat arbitrary. Actually the temperature at which the partial pressures of the components of the mixture are equal should be chosen, but the choice between the two would become important only if a much more efficient fractionation than used here is made. It is believed that an accuracy of ± 5 per cent is attained by this method. The accuracy of the method of analysis using the refractive index of the mixture is also believed to be of the order of ± 5 per cent, since precautions were taken to

remove, by washing and distillation, peroxides, antioxidants, polymerization products, and other contaminants.

In Table 2 are given the results of the experiments with isobutylene and hydrogen bromide. Run number 1, with an antioxidant, diphenylamine, gave a practically quantitative yield of tertiary butyl bromide, as was to be expected from previous studies of this reaction, especially by Shane.¹ In experiments 2, 3, and 4, high yields of isobutyl bromide were obtained when ascaridol was present in the reaction mixture. Run number 4 is felt to be particularly significant in that larger quantities of the reagents were used, with a consequent larger amount of product resulting. This made more accurate analyses possible, and justifies the statement that in the presence of peroxides and under the conditions of the experiments, practically quantitative yields of isobutyl bromide are obtained. These experiments were all run in the presence of air. Judging from this and from the difficulty which was experienced by Shane² in obtaining isobutyl bromide under any conditions, it is believed that the reaction of hydrogen bromide with isobutylene is relatively insensitive to the effect of peroxides.

The remarks given previously concerning the interpretation of the headings in Table 1 apply similarly to Table 2.

The data given in Table 3 summarizing the work on the reaction of pentene-1 with hydrogen bromide are clear cut in the case of runs numbers 1 and 2 where ascaridol was present and in numbers 5 and 6 where diphenylamine was present. Practically quantitative yields of 1-bromopentane were obtained in the presence of

¹Shane, op. cit.

²Ibid.

TABLE 2
ADDITION OF HYDROGEN BROMIDE TO ISOBUTYLENE

Run Number	Grams Isobutylene	Grams HBr	Grams Catalyst	Hours Reaction Time	Product Yield Percentage	Refractive Index Product	Boiling Point of Product versus Percentage Distilled				Percentage Isobutyl Bromide in Product
							10%	30%	70%	90%	
1	16.0	33	1.5 Diphenyl Amine	5	91	1.4275	73.3	73.4	73.4	73.4	20 n _D b.p.
2	12.1	29.3	1.5 Ascari- dole	4.5	92	1.4335	84.0	87.5	90.5	91.3	75 90
3	3	4.5	0.3 Ascari- dole	4	92	1.4347	87.1	87.4	89.7	91.2	90 95
4	46.4	91	6.0 Ascari- dole	1.7	96	1.4350	87.8	89.2	90.9	91.2	95 98

peroxides, and, as was found previously by Beck,¹ the reaction yielded only 2-bromopentane in the presence of antioxidants.

The data in the case of runs 3 and 4 are not conclusive. In the case of number 3, no 1-bromopentane was formed. A lack of homogeneity, due to the separation of solid acetic acid, was noted during the addition of hydrogen bromide, because of the necessary low temperature (-80°) of the mixture during this stage of the experiment. Because a lack of homogeneity in the reaction mixture had previously led to difficulties, it was decided to use propionic acid, which has a melting point about 40° lower than that of acetic acid. Although present to a lesser extent, a lack of homogeneity was observed. In this case about 40 per cent of the peroxide catalyzed product was obtained. The results do not warrant the unqualified statement that solvents have no effect on the reaction, although it seems possible that if hydrogen bromide were added under pressure at room temperature to pentene-1 in acetic or propionic acid in the presence of peroxides, complete reversal of the normal addition might take place. It is assumed that the reaction mixture would remain homogeneous under these conditions.

The remarks on interpretation of table headings applying to Table 1, apply to table 3, also. The figures in subcolumn under " D_{40}^{20} " appearing under the column "Percentage 1-Bromopentane in Product," were calculated from the densities of the pure components as given in "Experimental Part." It is assumed that the density of the mixture is a first-degree function of the densities of the components. The anilide derivatives were prepared by the method of Lauer and Stodola.²

¹Beck, op. cit.

²Lauer and Stodola, J. Am. Chem. Soc., **56**, 1215 (1934).

TABLE 3
ADDITION OF HYDROGEN BROMIDE TO PENTENE-1

Run Number	Grams Pentene-1	Grams HBr	Grams Catalyst	Grams Solvent	Hours Reaction Time	Product Yield Percentage	n _D ²⁰ Product	D ₄₀₀ ²⁰ Product	Boiling Point of Product versus Percentage Distilled				Percentage 1-Bromopentane in Product	
									10%	30%	70%	90%	n _D ²⁰	b.p.
1	10.5	16.8	1.0 Ascaridole		16	96	1.4442	1.2183	127.2	128.9	129.0	129.0	95	95
2	11.9	15.4	1.4 Ascaridole	12 Pentane	15	81	1.4443	1.2183	128.3	128.7	128.9	129.0	95	98
3	10.9	16.2	1.9 Ascaridole	19.6 Acetic Acid	12	51	1.4410		118.3	118.4	119.5		5	5
4	12.0	18.1	1.5 Ascaridole	18.7 Propionic Acid	20	89	1.4423	1.2084	120.3	121.4	124.7	130	40	40
5	11.6	19.4	0.4 Diphenylamine	11.4 Pentane	16a	81	1.4410	1.2035	118.1	118.2	118.2	118.2	5	2
6	9.9	17.2	0.5 Diphenylamine	14.0 Propionic Acid	14b	80	1.4410	1.2053	118.1	118.2	118.2	118.2	5	2

^aMP anilide 94.000.

^bMP anilide 90.6-92.400.

EXPERIMENTAL

Preparation of olefins.--The butene-1 was prepared essentially by the method of Lucas and Dillon,¹ from methylmagnesium chloride and allyl bromide. The methyl chloride was scrubbed with 85 per cent phosphoric acid and led into 1.5 l. of ether containing 50 g. magnesium. The flask was provided with a mercury seal stirrer and reflux condenser. Upon the completion of the reaction, the Grignard solution was filtered into another flask. The ether was distilled off and 210 g. allyl bromide (b.p. 69.8°) were added; 65 g. of butene-1 were evolved. This was condensed and then fractionally distilled through an 8-ball Snyder column. A fraction, boiling at -4.5°, was collected. This fraction constituted about 90 per cent of the charge. The final yield of butene-1, based on the allyl bromide, was 82 per cent.

The isobutylene was prepared by catalytic dehydration of tertiary butyl alcohol (b.p. 79.6°) with Baker's C.P. anhydrous oxalic acid. Equimolal proportions were used. The isobutylene was obtained in 87 per cent yield, and was fractionally distilled in a manner similar to that used above with the butene-1. The boiling range was -6.5 to -6.3°.

The pentene-1 was prepared from ethylmagnesium bromide and allyl bromide, in a manner similar to that used in preparing butene-1. A yield of more than 90 per cent was obtained of pentene-1 boiling at 29.5-33°. This material was treated with bromine at -10°, 1,2-dibromopentane being thereby obtained in 41 per cent yield, based on allyl bromide. The dibromide boiled at

¹Lucas and Dillon, J. Am. Chem. Soc., 50, 1460 (1928).

82.5-83.5° at 25.3 mm Hg; n_D^{20} 1.5087. This was decomposed with zinc in alcohol solution. The product was fractionated. 71g (34 per cent yield based on allyl bromide) was obtained which boiled at $29.5 \pm 0.05^\circ$ at 750 mm Hg; n_D^{20} 1.3712.

The hydrogen bromide was prepared by means of the reaction of boiling tetralin with Baker's C.P. bromine. The hydrogen bromide was passed over red phosphorus to remove bromine and then dried by passing over phosphorus pentoxide.

Preparation and Analysis of Reaction Mixtures.--The addition reactions were carried out in sealed glass tubes, using the technique developed by Kharasch and Mayo.¹ The reagents were condensed in these tubes at appropriately low temperature. The air was removed at this point by pumping if it was desired to avoid possible effects due to oxygen. The reagents were mixed at this same low temperature, and the container was sealed. The reaction tube and contents were then allowed to warm up to room temperature. After the time indicated in the table the contents of the tube were cooled, removed, and distilled at a pressure of about 25 mm., to separate product from peroxides, antioxidants, solvents, and the like, and then fractionally distilled through an 8-ball Snyder fractionating column. An air jacket surrounding the column minimized heat losses.

Any small amount of unreacted olefin or hydrogen bromide still remaining in the reaction mixture was removed through the column as a first fraction. The middle fraction consisting of the alkyl bromides was next removed. The vapor temperatures of the distillate were noted during this part of the distillation,

¹Kharasch and Mayo, J. Am. Chem. Soc., 55, 2486 (1933).

and were plotted as explained previously to determine the percentage of each constituent. The material remaining undistilled consisted of any polymerization products, et cetera, not removed in the previous vacuum distillation. The refractive index, and in the case of the bromopentanes, the density, of the middle fraction were measured. The refractive indices were determined using an Abbé type refractometer, and the densities were determined with pycnometers capable of an accuracy of ± 0.0001 . The anilides were prepared by means of the reaction of phenyl isocyanate with the bromides, according to the method of Lauer and Stodola.¹

The properties of the butyl and amyl bromides, which were used in the analyses of the reaction products, are given below.

	$n_D^{20^\circ}$	$D_4^{20^\circ}$	b.p.°C	m.p. of anilide°C.
1-Bromobutane	1.4395		101.0	
2-Bromobutane	1.4369		90.5	
Isobutyl bromide	1.4355		91.5	
Tert-butyl bromide	1.4276		72.0	
1-Bromopentane	1.4440	1.2175	129.7	124.9
2-Bromopentane	1.4411	1.2039	118.5	94.0

SUMMARY

It has been shown that in the absence of added peroxides, hydrogen bromide adds to butene-1, isobutylene and pentene-1 in such a way that the bromine becomes attached to the carbon atom carrying the least number of hydrogen atoms. No influence from solvents was detected.

In the presence of peroxides, hydrogen bromide adds in the

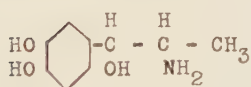
opposite direction to butene-1 and isobutylene, whether or not solvents are present. In the case of pentene-1, 1-bromopentane is formed in the absence of solvents and when pentane is used as the solvent. When acetic acid was used as the solvent 2-bromopentane was obtained and when propionic acid was used a mixture of 1 and 2-bromopentanes resulted. It is believed that a lack of homogeneity of the reaction mixture, with an attending separation of the peroxide from the olefin, due to the necessary low temperature of the reaction mixture during the addition of the hydrogen bromide, might account for the formation of the 2-bromopentane under these conditions.

THE PREPARATION OF SEVERAL INTERMEDIATES IN
THE SYNTHESIS OF 1-(3,4-DIHYDROXYPHENYL)
-1-HYDROXY-2-AMINOPROPANE

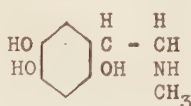
INTRODUCTION

The preparation of 3,4-dihydroxyphenylpropanolamine has been accomplished on a small laboratory scale by methods eminently suited for the purpose of obtaining quantities large enough for investigation of its therapeutic value. These methods have been expensive and laborious. The purpose of this work was to develop a simpler and more economical method of preparation.

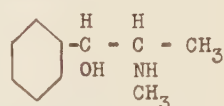
It has been shown¹ that 3,4-dihydroxyphenylpropanolamine (I) has sympathomimetic properties. It is claimed to have advantages over the widely used 1-epinephrine (II) and 1-ephedrine (III). The outstanding disadvantages of II and III are respectively, a lack of activity when taken orally, and a fairly high toxicity.



I



II



III

In general, pressor activity is characteristic of aromatic compounds having an aliphatic side chain of at least two carbon atoms and containing an amino group on the second carbon atom.²

¹German patents 216640, 254438, 269327; Tiffeneau, Compt. rend., 161, 36 (1915); Hartung, Munch, Miller, and Crossley, J. Am. Chem. Soc., 53, 4149 (1931).

²Hartung and Munch, ibid., p. 1875; Alles, J. Am. Med. Assn. 94, 790 (1930).

If the side chain is increased to three carbon atoms in length the compound becomes active when taken orally.¹ Toxicity is increased when the side chain is increased to four or more carbon atoms, or when the size of the groups attached to the amino nitrogen is increased.²

This subject of the relation of structure to physiological activity has been reviewed in great detail by W. H. Hartung.³

PREVIOUS WORK

3-4-Dihydroxyphenylpropanolamine was first prepared in 1908⁴ by the condensation of dimethyl ether of catechol with 2-phthalimidopropionyl chloride with the aid of aluminum chloride. The methyl and phthalic acid groups were removed by hydrolysis with hydrochloric acid, and the amino alcohol was obtained by hydrogenation of the resulting ketone.

Hartung and co-workers⁵ prepared 3,4-dihydroxypropanolamine by nitrosating the 3,4-dihydroxypropiophenone with butyl nitrite and hydrogenation of the resulting oximino ketone. Their tests of the racemic mixture showed that it was about one-twelfth as active and one-hundredth as toxic as epinephrine when given

¹Hartung, Munch, Deckert, and Crossley, J. Am. Chem. Soc., 52, 3317 (1930); Piness, Miller, and Alles, J. Am. Med. Assn., 94, 790 (1930).

²Chen, Wir, and Henricksen, J. Pharmacol., 36, 363 (1929); Curtis, ibid., p. 321.

³Hartung, Chem. Rev., 9, 389 (1931).

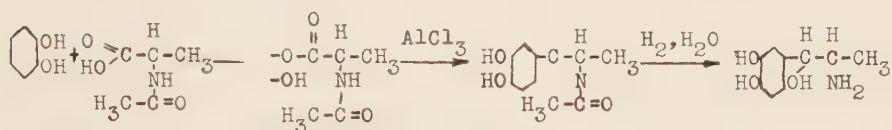
⁴German patents 216640, 254438, 269327.

⁵Hartung, Munch, Miller, and Crossley, J. Am. Chem. Soc., 53, 4149 (1931).

intravenously. It was also shown that the substance had a high oral activity.

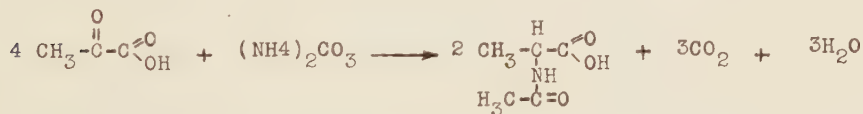
PRESENT WORK

While the above methods described above have been successful in the preparation of the substance in small amounts, a less expensive synthesis was, however, desired. It was hoped that the following sequence of reactions would yield the desired product:



THE PREPARATION OF ACETYLALANINE

Great difficulties were encountered in the acetylation of alanine. All preliminary attempts to acetylate either alanine or its ethyl ester with acetic anhydride or acetyl chloride were in vain; gummy resinous materials resulted in all attempts. Several references to the preparation of acetylalanine from pyruvic acid and ammonium carbonate appear in the literature.¹



The yield, using this method, was about 10 per cent, and consequently unsatisfactory. The material obtained by this method melted at 110-125° and after crystallization from water, at 136.5-137.5°. I have found that a satisfactory yield (75 per cent) of

¹Fischer, *Ber.*, 36, 2115 (1903); Mohr, *J. prakt. Chem.* (2) 82, 63 (1910); de Jong, *Rec. trav. chim.*, 19, 282-88 (1900).

acetylalanine may be obtained from pyruvic acid and ammonium hydroxide.

PREPARATION OF ACETYLALANINE

To 340.7 grams pyruvic acid (b.p. $63-68^{\circ}$ at 14 mm., n_D^{20} 1.4284), obtained from Eastman Kodak Company pyruvic acid by distillation at 14 mm. was added the equivalent amount (950 cc.) 2.0 M ammonium hydroxide. The mixture was placed on a steam bath. The temperature rose quickly to 94° . A vigorous evolution of carbon dioxide took place. After eight hours on the steam bath the evolution of carbon dioxide had practically ceased. The solution was concentrated in vacuo to about 300 cc., and placed in the refrigerator for thirty-six hours. A large quantity of crystals had separated. These were collected on a filter and washed with a very small amount of ice water. This material was dried at 100° in high vacuo (0.02 mm.). The weight of dry material was 138 grams (54 per cent of the calculated yield). The melting point was $136.6-137.6^{\circ}$. By working up the mother liquor, the yield was raised to approximately 75 per cent.

THE PREPARATION OF THE CATECHOL ESTER OF ACETYL ALANINE

Preliminary attempts to prepare the acid chloride of acetylalanine were unsuccessful. Resinous materials were the main products. Attempts to prepare the ester from catechol, acetylalanine, and thionyl chloride, without solvent and with benzene as a solvent, were unsuccessful. However, dioxane appeared to be a suitable solvent. Accordingly, 3.6 grams thionyl chloride in 15 cc. dioxane were added to a refluxing solution of 4.0 grams acetylala-

nine and 3.4 grams catechol in 50 cc. dioxane, over a period of five yours. The solution was evaporated, and the residue extracted with ether.¹ Upon evaporation of the ether, 0.8 g. of a crystalline material separated. The melting point was 130-135°. When crystallized from water, 0.7 grams of material melting at 135.6-136.3° was obtained. A considerable depression in the melting of this material was observed when 10 per cent acetyl alanine was added to it (115-130°). Upon recrystallization, first from toluene and then from dioxane, the melting point was raised to 137.8°.

Anal., Calc. for $C_{11}H_{13}O_4N$, %N, 6.28. Found 5.99, 5.85.

A large quantity of this material was prepared as follows: To a refluxing solution of 55 grams of catechol (0.5 mole) and 65.5 grams (0.50 mole) of acetyl alanine in 250 cc. dioxane, 63.5 grams (0.53 mole) of thionyl chloride in 30 cc. dioxane were added over a period of 40 minutes. The refluxing was continued for 1.3 hours. Half of the dioxane was removed by distillation and 125 cc. of toluene and 2 cc. of methyl alcohol were added. After placing this solution in the refrigerator an oil separated which later crystallized. About 1 cc. of a viscous oil was removed from these crystals by heating at 100° for four hours at about 0.01 mm. The reaction mixture was purified as described in the first preparation and was obtained in 42 per cent yield.

¹Acetylalanine is not soluble in ether.

SUMMARY

A satisfactory method of preparing acetylalanine in 70-80 per cent yield from ammonium hydroxide and pyruvic acid has been developed.

The monocatechol ester of acetyl alanine has been obtained in 42 per cent yield from the reaction of acetylalanine and catechol in the presence of thionyl chloride.

